REMARKS

This Amendment and Remarks are filed in response to the Office Action dated November 1, 2007.

Applicants apologize for previously providing incorrect identification of pages and lines of the support for the previously pending claims 63-82 in Status of Claims. Applicants have two printouts of the application and apparently the wrong printout was used in identifying the relevant pages and lines. To avoid the same mistake, Applicants now identify the paragraphs in the printed published application US 2004/0151705 A1.

Status of the Claims

Claims 1-63, 68, 72 and 78-82 are canceled. New claim 83 is added.

The new claim 83 and amended claims 64-67, 69-71 and 73-77 are supported as follows:

Claim 83, preamble: An implantable construct[0078] consisting essentially of a newly developed immature hyaline cartilage [0075] comprising a support matrix embedded [0183] with activated chondrocytes [0078] and an extracellular matrix produced by said activated chondrocytes wherein a ratio of extracellular matrix to chondrocytes is lower than 95:5% [0123], [0124] and [0119] and wherein said chondrocytes are rejuvenated chondrocytes [0124] activated from inactive non-dividing chondrocytes [0117] to activated chondrocytes by repeatedly applying to inactive non-dividing chondrocytes embedded in said matrix a cyclic hydrostatic pressure [0084] followed by a resting period at constant atmospheric pressure [0252], wherein said activation results in

cell propagation [0074], production of DNA [0208] and production of extracellular matrix macromolecules Type II collagen and S-GAG [0208];

wherein said cell proliferation is a result of activation of said inactive non-dividing chondrocytes into the newly developed immature hyaline cartilage containing active, dividing and multiplying chondrocytes [0208],

wherein said production of DNA is a result of a genetic activation of said inactive non-dividing chondrocytes [0208],

wherein said Type II collagen and S-GAG are produced by the extracellular matrix synthesized by said activated chondrocytes [0208],

wherein said inactive non-dividing chondrocytes are mature chondrocytes unable, without activation, to divide, multiply and synthesize the extracellular matrix macromolecules [0124] and wherein said chondrocytes are isolated from a human donor's joint cartilage [0127] by enzymatic digestion [0356], expanded by culturing in a culture medium [0357], suspended in a collagen containing solution [0360], gel or thermo-reversible hydrogel [0138] and [0143] and seeded into the support matrix as a suspension of said inactive non-dividing chondrocytes [0142],

wherein said support matrix is a sponge, scaffold, honeycomb or lattice [0074], [0149], prepared from a material selected from the group consisting of a Type I collagen; Type II collagen; Type IV collagen; a collagen containing glycosaminoglycan, agarose or hyaluronin; a collagen containing proteoglycan, glycoprotein, gelatin, fibronectin, laminin, bioactive peptide, growth factor or cytokine; and a synthetic polymeric fiber made of a polylactic

acid, polyglycolic acid, polyamino acid or polycaprolactone [0151],

wherein said sponge, scaffold, honeycomb or lattice, each contains a plurality of pores having a size ranging from about 100 μm to about 300 μm [0149],

wherein said support matrix seeded with said inactive non-dividing chondrocytes is subjected to the activation with a cyclic hydrostatic pressure from about 0.5 MPa to about 5 MPa [0192] above atmospheric pressure applied at a frequency of from about 0.01 to about 2 Hz [0192], for from about one hour to about 30 days [0192], followed by a resting period from about one day to about sixty days [0192], said activation repeated for from about one week to about three months [0124],

wherein during said activation said support matrix seeded with said chondrocytes is further subjected to a perfusion with a perfusion medium at a flow rate from about 1 to about 50 μL per minute [0189],

wherein said activation results in converting said inactive non-dividing chondrocytes into activated chondrocytes that divide, multiply and synthesize said extracellular matrix macromolecules thereby forming said implantable construct, wherein said formed implantable construct comprises more than 5% of activated chondrocytes and a ratio of the newly synthesized extracellular matrix to activated chondrocytes is lower than 95:5% [0123].

Claim 64 is supported in [0151]

Claim 65 is supported in [0151]

Claim 66 is supported in [0192]

Claim 67 is supported in [0192]

Claim 68 is canceled

Claim 69 is supported in [0189]

Claim 70 is supported in [0196]

Claim 71 is supported in [0196]

Claim 72 is canceled

Claim 73 is supported in [0153]

Claim 74 is supported in [0189]

Claim 75 is new

Claims 76-82 are canceled

In the Preliminary amendment claim 75 was missing, apparently due to a clerical error, and consequently applicants canceled Claim 76 and added new Claim 75. That claim is supported in [0127].

Rejections under 35 USC § 112, First Paragraph

Claims 63-82 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors at the time the application was filed, had possession of the claimed invention.

Examiner submits that support is not readily apparent in the specification for isolating chondrocytes from joint cartilage in step a) of claims 63 and 78, the alternatives of a collagen containing solution, gel and thermo-reversible hydrogel in step c) of claim 63, the alternative of a collagen containing solution and thermo-reversible hydrogel. In step c) of claim 78, the alternatives of a collagenous sponge, collagenous scaffold, collagenous honeycomb and collagenous honeycomb-like lattice required by lines 37-38 of claims 63 and 78, the alternatives of a

collagenous sponge and collagenous honeycomb in claim 78, for "about five to about ten days" and "about ten to about fourteen days" in lines 23 and 24, respectively, of claim 78, and for a combination-of types I, II and IV collagen as required in the last line of claim 79. The page and line of the specification where each of the above claim limitations is recited should be pointed out.

Support is not found in the pages and lines recited on page 9 of the amendment.

Support is not found in the specification for a Markush group of alternative materials for preparing the support matrix as required by claim 64. The page and line should be pointed out where each member of the group is recited, and the members being in a combination as required by the last line of the claim. Support is not found in the pages and lines recited on page 9 of the amendment.

Applicants disagree. Support for these claims is present in the specification. However, in view of the claim amendment, Applicants provide a correct information regarding all pending and amended claims in the Status of Claims section, above.

Rejections under 35 USC § 112, Second Paragraph

Claims 63-82 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Bridging lines 5 and 6 of claims 63 and 78, "genetically activated" is uncertain as to meaning and scope. The steps

subsequently required for activation do not appear to be steps that would normally be considered to be "genetically".

Applicants disagree. Increased level of DNA production shows genetic activation of inactive chondrocytes. Increased levels of DNA production is shown, for example in Table 2 and also in Figure 13A.

Claims 63 and 78 are confusing by further defining conditions of steps a) and d) near the end of the claims in lines 31-39 separate from where the steps initially required. All conditions of steps a) and d) should be set forth where the steps are initially required.

Applicants disagree, however, in order to advance the examination, Applicants redrafted claims as suggested.

Claims 63 and 78 are unclear in lines 25 and 26 as to material in the activation step the perfusion medium contacts when perfusion is performed.

Applicants disagree. Both claims 63 and 78 are canceled However, to make the perfusion step more definite, applicants have introduces the following language in claim 83 "wherein during said activation said support matrix seeded with said chondrocytes is further subjected to a perfusion with a perfusion medium at a flow rate from about 1 to about 50 µL per minute". Applicants believe that this amendment meets Examiner's concerns.

In line 38 of claims 63 and 78, "honeycomb-like" is uncertain as to meaning and scope. Being like a honeycomb is relative and subjective.

Applicants disagree. The term used is not "honeycomb-like" but "honeycomb-like lattice". The new claim 83 does not use this term.

Bridging lines 7 and 8 of claim 64, "collagen containing a synthetic polymeric fiber made of a polylactic acid" is uncertain how collagen can contain a synthetic polymeric fiber made of polylactic acid. The specification fails to describe collagen containing a fiber as claimed.

Applicants disagree. However, to meet Examiner's rejections, applicants amended claim 64.

Claim 77 is confusing by requiring the matrix to be seeded with isolated and expanded chondrocytes since this is already required in claim 63. Repeating in a dependent claim conditions that are already in an independent claim makes unclear how the dependent claim further limits the independent claim.

Applicants disagree, however, to expedite the prosecution, applicants canceled claim 77.

Applicants believe that with the new amendment, rejections under 35 USC 112, second paragraph are overcome.

Rejections under 35 USC § 102

Claims 63-82 are rejected under 35 U.S.C. 102(a) as being anticipated by Smith et al (6,528,052).

Examiner argues that the claims are drawn to an implantable construct suitable for implantation into a cartilage lesion or defect. The construct is prepared by isolating inactive chondrocytes from joint cartilage by subjecting the cartilage to enzymatic digestion, expanding the chondrocytes in a culture medium, suspending the expanded chondrocytes in a collagen solution, gel or thermo-reversible hydrogel, seeding the suspension in a support matrix which is a collagenous sponge, scaffold,

honeycomb or honeycomb-like lattice having pores 50 to 500 μm in size. The seeded support is subjected to an activation step for about one week to about three months, which comprises applying to the seeded support a cyclic hydrostatic pressure from about 0.01 to 10 MPa above atmospheric pressure at a frequency of from about 0.01 to 2 Hz for about one hour to 30, days followed by a resting period from about one day to sixty days. During activation, perfusion with a perfusion medium is performed at a flow rate from about 1 to 500 μL per minute. The formed construct comprises more than 5% of activated chondrocytes, and has a ratio of newly synthesized extracellular matrix to activated chondrocytes in the construct lower than 95:5.

Examiner argues that Smith et al disclose repair and regeneration of cartilage by a process that involves in vivo, ex vivo or in vitro treatment of cartilage or cartilage cells (chondrocytes) in a support such as a scaffold or collagen matrix (col 6, lines 14-16) by using a loading regiment involving conditions of intermittent application of periods of hydrostatic pressure followed by periods of recovery in situ (col 4, lines 25-31, and col 7, line 30 to col 8, line 8). The recovery period can be at atmospheric or low constant pressure (col 7, lines 48-50). *In vitro* treatment is performed by obtaining cartilage cells from cartilage, and applying the loading regiment conditions while culturing the cartilage cells in suspension within a scaffold/support, and implanting the resultant tissue or cells into a patient (col 9, 20 lines 23-30, and col II, lines 5-9). Articular chondrocytes (col 16, line 65) are isolated from cartilage using enzyme digestion (col 17, lines 41- 43).

Examiner concludes that a cartilage construct produced by the process of Smith et al is the same construct presently claimed for implantation into a cartilage lesion or defect. No difference is seen in the presently claimed process from the process of Smith et al that would result in a materially different construct. The process of Smith et al will inherently produce a construct having at least 5% activated chondrocytes, and a ratio of newly synthesized extracellular matrix to activated chondrocytes lower than 95:5.

Applicants disagree. Anticipation requires that the subject matter in its entirety is disclosed in the prior art. To anticipate a claim, the reference must teach every element of the claim (MPEP 2131): "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." Verdegaal Bros. vs Union Oil Co. Of California, 814 F. 2d 628 at 631, 2USPQ2d 1051, at 1053 (Fed. Cir. 1987). Applicants respectfully submit that Smith does not disclose each and every element of the claim 83. Smith reference is directed to a regeneration and repair of damaged cartilage not to a construct consisting of a newly developed immature hyaline cartilage.

The new claim 83 is directed to an implantable construct that consists of a newly developed immature hyaline cartilage (Smith does not disclose immature or hyaline cartilage or a construct consisting of such cartilage) comprising a support matrix embedded with activated chondrocytes (Smith does not disclose activated chondrocytes) and an extracellular matrix produced by said activated chondrocytes wherein a ratio of extracellular matrix to

chondrocytes is lower than 95:5% (Smith does not disclose any ratio of chondrocytes to the extracellular matrix) wherein said chondrocytes are rejuvenated chondrocytes (Smith does not disclose rejuvenated chondrocytes) activated from inactive non-dividing chondrocytes to activated chondrocytes by repeatedly applying to inactive non-dividing chondrocytes (Smith does not disclose applying hydrostatic to inactive non-dividing chondrocytes) embedded in said matrix a cyclic hydrostatic pressure followed by a constant atmospheric pressure, wherein said activation results in cell propagation and proliferation (Smith does not disclose cell propagation or proliferation), production of DNA (Smith does not disclose DNA production) and production of extracellular matrix macromolecules Type II collagen and S-GAG;

wherein said cell proliferation is a result of activation of said inactive non-dividing chondrocytes into the newly developed immature hyaline cartilage containing active, dividing and multiplying chondrocytes (Smith does not disclose this element),

wherein said production of DNA is a result of a genetic activation of said inactive non-dividing chondrocytes (Smith does not disclose this element),

wherein said Type II collagen and S-GAG are produced by the extracellular matrix synthesized by said activated chondrocytes,

wherein said inactive non-dividing chondrocytes are mature chondrocytes unable, without activation, to divide, multiply and synthesize the extracellular matrix macromolecules (Smith does not disclose mature non-dividing cells or their activation) and wherein said chondrocytes are isolated from a human donor's joint cartilage by enzymatic digestion, expanded by culturing in a culture medium,

suspended in a collagen containing solution, gel or thermo-reversible hydrogel and seeded into the support matrix as a suspension of said inactive non-dividing chondrocytes,

wherein said support matrix is a sponge, scaffold, honeycomb or lattice (Smith does not disclose sponge, honeycomb or lattice), prepared from a material selected from the group consisting of a Type I collagen, Type II collagen, Type IV collagen, a collagen containing glycosaminoglycan, agarose or hyaluronin; a collagen containing proteoglycan, glycoprotein, gelatin, fibronectin, laminin, bioactive peptide, growth factor or cytokine; and a synthetic polymeric fiber made of a polylactic acid, polyglycolic acid, polyamino acid or polycaprolactone (Smith does not disclose support matrix made of the above materials, not even such as Type I, Type II or Type IV collagens used for preparation of a support matrix),

wherein said sponge, scaffold, honeycomb or lattice, each contains a plurality of pores having a size ranging from about 100 μm to about 300 μm (Smith does not disclose a support matrix requiring having predetermined pore size),

wherein said support matrix seeded with said inactive non-dividing chondrocytes is subjected to the activation with a cyclic hydrostatic pressure from about 0.5 MPa to about 5 MPa above atmospheric pressure applied at a frequency of from about 0.01 to about 2 Hz, for from about one hour to about 30 days, followed by a resting period at a constant atmospheric pressure from about one day to about sixty days, said activation repeated for from about one week to about three months,

wherein during said activation said support matrix seeded with said chondrocytes is further subjected to a perfusion with a perfusion medium at a flow rate from about 1 to about 50 µL per minute (Smith does not disclose perfusion),

wherein said activation of said chondrocytes is additionally performed under a reduced oxygen concentration of less than 20% or 2% (Smith does not disclose use of oxygen or carbon dioxide),

wherein said activation results in converting said inactive non-dividing chondrocytes into activated chondrocytes that divide, multiply and synthesize said extracellular matrix macromolecules thereby forming said implantable construct (Smith does not disclose conversion of inactive, non-dividing cells into active and dividing cells) wherein said formed implantable construct comprises more than 5% of activated chondrocytes and a ratio of the newly synthesized extracellular matrix to activated chondrocytes is lower than 95:5 (Smith does not disclose ratio of chondrocytes to the extracellular matrix),

wherein said construct is implanted into a cartilage lesion and results in a full integration of said newly developed hyaline cartilage into a cartilage surrounding said lesion (Smith does not disclose any histological results or integration of newly prepared hyaline cartilage into a cartilage lesion).

Applicants submit that the construct is not described in the cited Smith reference as required by 35 USC 102 (a) and, moreover, the construct of the invention is not inherently described. The fact that the inactive non-dividing cells may be activated into cells that multiply and proliferate into a hyaline cartilage is nowhere described, suggested or implied. At most, the instant

invention and claims can be said to be directed to an improvement of the Smith's method. As evidenced by a full integration of said construct into hyaline cartilage of the treated lesion as described in the instant application and can be seen in Figures 12 and 13, the instant construct provides means for such full integration by providing a matrix having predetermined pores permitting said inactive chondrocyte when activated to proliferate and propagate in 3-dimensions and wherein such proliferation continues after implantation of said construct into the lesion to result in full integration into a surrounding cartilage.

Applicants respectfully submit that the instant claim 83 and dependent claims not anticipated and the rejection should be withdrawn.

Rejections under 35 USC § 103

Claims 63-82 are rejected under 35 U.S.C. 103(a) as being unpatentable over Smith et al (6,528,052) in view of Lee et al (6,306,169) and Burg (6,991,652), and if necessary in further view of Atkinson et al (6,511,958).

The invention and Smith et al are described above.

Examiner argues that Lee et al disclose producing an implant containing cells such as chondrocytes (col 7, line 8) by isolating the cells from tissue, proliferating the cells in a medium containing serum to obtain a sufficient number of cells, and seeding the cells in a construct (col 7, lines 13-17) such as a collagen sponge (col 12, line 17). A collagen sponge can be infiltrated with an alginate or agarose solution containing the cells, and the alginate or agarose gelled within the sponge (col

13, lines 11-25). This procedure produces a construct having mechanical function that resembles that processed by tissue to be repaired (col 4, lines 28-37) and further that Burg discloses forming a hydrogel-·cell composition for use in forming new tissue such as cartilage. Before the cell are incorporated in a construct, the cells can be expanded in number by culturing *in vitro* in a medium containing serum (col 7, lines 20-29). Temperature-dependent hydrogels can be used (paragraph bridging cols 5 and 6). The hydrogels have reverse gelation properties, and are liquids at or below room temperature, and gel when warmed to higher temperatures, e.g. body temperature.

When incorporating chondrocytes from cartilage into a scaffold for treatment as disclosed by Smith et al, it would have been obvious to expand the number of cells by *in vitro* culturing in a culture medium prior to incorporating the cells in the scaffold as suggested by Lee et al and Burg expanding the number of cells before incorporating the cells in a scaffold for implanting. The resultant construct will be a cartilage construct as presently claimed, and will inherently have a ratio of newly synthesized extracellular matrix to activated chondrocytes of lower than 95:5.

Smith et al disclose using a hydrostatic pressure and frequency of applying the pressure that are the same or substantially the same as used in the present claims. Perfusion with a medium as claimed during treatment with hydrostatic pressure would have been obvious to provide nutrients for the cells to maintain the cells active for growth. Suspending the chondrocytes of Smith et al in a solution such as a collagen solution before seeding the cells in the matrix is suggested by Lee et al (col 6, line 21, and col 13, lines 11-26) that forms a second matrix

component. The collagen solution would have been expected to gel and form a scaffold for the chondrocytes.

The conditions of dependent claims are suggested by conditions used by the references. Lee et al suggest a sponge and Burg suggests temperature-dependent hydrogels as a matrix for seeding cells to implant. Air contains slightly above 20% oxygen and using slightly less than 20% oxygen as in claim 70 would have been an obvious variation that would not be expected to produce a difference in result. Smith et al disclose 7.5% carbon dioxide (col 17, line 10), and using 5% as in claim 71 is an obvious variation that would not be expected to produce a difference in result.

Atkinson et al further disclose repairing cartilage lesions, and if needed would have further suggested conditions that can be used.

Applicants disagree. Examiner does not consider the instant invention and claims in their entirety, and disposes of certain conditions that are necessary for practicing the instant invention in order to get the claimed construct without regard for their significance.

For example, the perfusion flow between 5 and 50 µl/minute has a great effect on production of S-GAG, as seen in Table 3, paragraph [0239]. At 50 µl/ minute flow the production of S-GAG is 78.75± 6 compared to S-GAG production at 5 µl/min being 107.10±, resulting in a substantial increase of production of extracellular matrix macromolecules. Similarly, concentration of oxygen has effect on S-GAG production as seen in Table 4 paragraph [0247] where the production of S-GAG at 20% of oxygen is 60.82± and increases to 105.59± when the oxygen concentration is lowered to about 2%. That is approximately 1.7 times higher production of S-

GAG per µg/cell in construct. None of the four references mentions oxygen concentration or recognize its importance for cell culturing.

Just these two above described facts clearly show that chondrocytes are activated and result in production of the immature cartilage of the instant invention having more then 5% chondrocytes and ratio of extracellular matrix to chondrocytes lower than 95:5%.

Examiner further states that Smith discloses 7.5% carbon dioxide and that variation between 7.5% and 5% of carbon dioxide is obvious variation that would not be expected to produce a difference in result. Examiner is recommended to review the col 17, line 23, where such alleged disclosure appears. Should Examiner do that he will find that the 7.5% of carbon dioxide is used for plating chondrocytes on tissue plates during cell isolation and culturing and not during the actual activation of inactive non-dividing chondrocytes, as claimed herein. Neither use of reduced oxygen or presence of carbon dioxide during the processing by Smith or culturing of Lee, Burg or Atkinson is disclosed. Such elements are used solely for activation of inactive non-dividing cells of the invention in the process of activation.

None of the cited references discloses inactive non-dividing chondrocytes that are activated to produce extracellular matrix and to multiply, propagate, proliferate and result in newly developed immature hyaline cartilage that is, upon implantation, integrated into the cartilage tissue surrounding the cartilage lesion or defect.

Examiner maintains that Smith and other references produce constructs that have inherently a ratio of chondrocytes to the extracellular matrix. Applicants respectfully submit that it is not

so. There would have to be some knowledge and evidence of such activation being possible of the inactive static cells to become active to the extent that they correspond to the immature active cells that produce extracellular matrix and result in development of the hyaline cartilage in young individuals. It is a cumulative combination of activation conditions as enumerated in claim 83 that results in production of the newly developed immature hyaline cartilage that, when implanted, is readily incorporated into the surrounding cartilage.

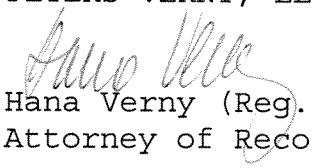
Applicants submit that the instant invention is not obvious from the cited references and should be withdrawn. It is so respectfully requested.

SUMMARY

In summary, applicants amended claims 64-67, 69-71, 73 and 74, added new claims 75 and 83, provide evidence of the support in the specification and provide arguments to overcome rejections under 35 USC 102 (a) and 103. It is believed that all rejections have been overcome and the instantly submitted claims are in condition for allowance. Notice of allowance is respectfully solicited.

Date: March 6, 2008

Respectfully submitted,
PETERS VERNY, LLP



Hana Verny (Reg. No. 30,518)
Attorney of Record

PETERS VERNY, LLP
425 Sherman Avenue, Suite 230
Palo Alto, CA 94306
TEL 650 324 1677 / FAX 650 324 1678
Atty. Dkt.: 3831.08
Customer No.: 23308